

# Urinary tract infection

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## Abstract

Urinary tract infection is one of the most common infections to affect humans. Uncomplicated infections most commonly occur in otherwise healthy women when uropathogenic bacteria, usually *Escherichia coli*, enter the bladder and overcome host innate immunity. Complicated infections occur in patients with an anatomical or functional abnormality of the urinary tract. Diagnosis is made on the basis of symptoms, and diagnostic precision is improved by urinalysis. Urine culture is important in patients with severe, recurrent or complicated infection and when diagnosis is uncertain, for example in children and elderly people. Most women with symptoms that resolve quickly do not require further investigation, but imaging of the renal tract, functional testing and cystoscopy should be considered in children, men and patients with recurrent or severe infection. Empirical antibiotic treatment started on the basis of symptoms and directed by urinalysis is suitable for uncomplicated cystitis but should be altered based on culture results for more severe infections. Three days of antibiotic treatment is usually sufficient for uncomplicated cystitis in women. Long-term or post-coital antibiotics are effective for patients with recurrent infection.

**Keywords** Antibiotics; cystitis; host defence; MRCP; pyelonephritis; urinary tract infection

## Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections, affecting 40% of women at some point in their life. UTI can cause life-threatening sepsis but most infections are less severe. Nevertheless, UTI causes the individual significant distress and is associated with high healthcare and social costs. In the USA, UTIs are responsible for 7 million clinic visits annually, with a cost >\$1.6 billion.

UTI is most commonly bacterial, but fungal, viral and parasitic infections can occur. Cystitis is the most common UTI, but infection can occur throughout the urinary tract, causing

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## Key points

- In non-pregnant women, uncomplicated cystitis with typical symptoms can be treated with 3 days of empirical antibiotics
- Urine culture is not always required. It is necessary in severe, complicated or recurrent infection, children, men, individuals >65 years old and those with risk factors for antibiotic resistance, and when the diagnosis is uncertain
- Men require longer (7 days) treatment because of the possibility of prostatitis or complicated infection
- Given its potential long-term adverse effects, ciprofloxacin should be prescribed only with caution for urinary tract infection (UTI)
- Asymptomatic bacteriuria requires treatment only in pregnancy and before urological procedures; screening should be restricted to these groups
- UTI can present non-specifically in the over-65s, including with delirium
- Urine dipstick testing should not be done in those aged over 65 as it does not add to the diagnosis. Instead, start antibiotics if the patient symptomatic, and send a urine culture before the first dose

pyelonephritis, urethritis and prostatitis. Asymptomatic bacterial colonization of the urinary tract is common in women and elderly individuals.

UTI can be classified as complicated or uncomplicated. Uncomplicated UTI occurs in the absence of anatomical or functional abnormalities within the urinary tract and is the most common type of infection. Complicated UTI occurs in the presence of an abnormal urinary tract or any other factor that increases susceptibility to infection. The common causes of complicated UTI are listed in [Table 1](#).

## Epidemiology

Asymptomatic bacteriuria is found in 1–2% of school-age girls and 5% of women but is rare in males. The prevalence increases with age, and bacteriuria is found in 21% of women and 12% of men aged >65 years and in >40% of people living in institutions. Acute uncomplicated cystitis is the most common form of symptomatic UTI, affecting 40% of women at some point in their life, and UTIs account for 25% of infections in the elderly population. One-third of patients who develop a UTI go on to have recurrent infections. Symptomatic infection is less common in men.

Nosocomial UTI is the most common hospital-acquired infection, most being catheter-associated. UTI develops in 25% of patients who require a catheter for over 7 days, with a 5% daily risk. UTI adds to the duration and cost of hospitalization, and nosocomial uropathogens form a reservoir of antibiotic-resistant bacteria.

### Common causes of complicated UTI

Bladder outflow obstruction
• Prostatic disease
• Urethral stricture
• Bladder neck obstruction
Neuropathic bladder
• Multiple sclerosis
• Diabetes mellitus
• Spina bifida
• Spinal cord trauma
Catheterization or stent
Renal tract stone disease
Instrumentation of the renal tract
Renal or urinary tract malignancy
Reflux
Duplex system
Ileal conduit
Pregnancy
Glycosuria
Kidney transplant
Immunosuppression

**Table 1**

### Aetiology

Under normal circumstances the urinary tract is sterile and infection develops only when bacterial virulence overcomes normal host defence mechanisms. *Escherichia coli* is the most common uropathogen in both hospitals and the community, with *Proteus mirabilis*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* each causing <10% of cases.

### Host factors

Sterility of the urinary tract is maintained by physical factors, including the unidirectional flow of urine, frequent and complete emptying of the bladder, separation of the bladder from a source of pathogens and reduced bacterial growth in urine. Contact between the urinary tract epithelium and bacteria induces an inflammatory response, activation of the innate immune system (especially neutrophils) and synthesis of antibacterial peptides (defensins, cathelicidins). The secretion of the P blood group antigen and Tamm–Horsfall protein (uro-modulin) interferes with bacterial adhesion to epithelial cells, and colonized epithelial cells are shed into the urine. Although there is evidence of an adaptive immune response in UTI (pathogen-specific immunoglobulin (Ig) A in the urine after infection), it is unclear whether it is important in the defence against further infection.

### Bacterial virulence factors

To overcome the flow of urine, uropathogenic bacteria express a series of fimbrial adhesions. Fimbriae are filamentous structures that project from the surface of the bacteria and are responsible for binding to the host epithelium. Uropathogens also produce toxins, haemolysin and colony-necrotizing factor, which disrupt epithelial integrity and permit bacterial invasion.

### Pathogenesis of infection

In most cases, the uropathogens originate in the rectal flora, and colonization of the perineum and periurethral area precedes the development of infection. Colonization is inhibited by the normal bacterial flora, including *Staphylococcus epidermidis*, lactobacilli and corynebacteria, which is disrupted by antibiotics and postmenopausal oestrogen deficiency. Uropathogens then use their fimbrial adhesions to ascend through the urethra to the bladder and kidney. The shorter length of the urethra and the proximity of the urethral meatus to the perineum explain the higher rate of infection in women.

Several factors are associated with risk of infection, including sexual activity, the use of a diaphragm and spermicide-based contraception, and a history of previous or recurrent UTI (Table 2). Fifty percent of women presenting with a UTI have a maternal history of UTI. Although associations between UTI and some genes (blood group secretor status, interleukin 8 receptor) have been reported, genetic factors influencing UTI risk are not fully understood.

### Complicated UTI

This occurs if there is an anatomical or functional abnormality of the renal tract (Table 1). The normal host defence is disturbed, so the requirement for virulence factors is reduced and the spectrum of pathogens increases. Disruption of the normal flow of urine or a foreign body within the urinary tract are the most frequent associations. Management should include treatment of the acute infection and, when possible, reversal of the underlying pathology.

### Clinical features of UTI

Colonization of the urinary tract, usually defined as  $>10^5$  bacteria/ml in freshly voided urine (although some guidelines adopt lower counts), causes a spectrum of clinical presentations. UTI, particularly in children and elderly individuals, may not present with typical symptoms, and the diagnosis can easily be missed.

**Asymptomatic bacteriuria** is the presence of  $>10^5$  bacteria/ml of urine in the absence of other features of infection. Asymptomatic bacteriuria increases the risk of developing symptomatic UTI; 8% of women with asymptomatic bacteriuria develop a symptomatic UTI within 1 week. In most

### Risk factors for UTI

Female gender
Complicated urinary tract anatomy
Incomplete bladder emptying
Recent or recurrent UTI
Sexual intercourse
Diaphragm and spermicidal contraception
Disruption of normal bacterial flora
• Recent antibiotic use
• Postmenopausal alteration in vaginal flora
Pregnancy
Family history of UTI
Non-secretor status (P blood group antigen)

**Table 2**

circumstances, asymptomatic bacteriuria does not require treatment. As it has limited prognostic significance, antibiotic use is unnecessary and the recurrence rate is high. However, in pregnant women asymptomatic bacteriuria is associated with an increased risk of pyelonephritis and low birthweight, so screening and treatment are indicated. Screening is also often performed before urological intervention.

**Cystitis** – bladder infection is the most common form of UTI. It typically presents with dysuria, frequency, urgency, suprapubic pain, haematuria and offensive or cloudy urine. Typical symptoms, when present, are sufficient to diagnose cystitis. Systemic symptoms such as fever, nausea and vomiting can occur.

**Pyelonephritis** – infection involving the renal parenchyma is usually caused by ascending infection from the bladder. In addition to local symptoms (loin pain, haematuria and possibly symptoms of cystitis (which are only present in 50% of cases)), systemic symptoms and signs are common and frequently severe, with fever, rigors, vomiting and septic shock. C-reactive protein and erythrocyte sedimentation rate are often raised, and blood cultures are positive in 20% of cases.

Although infection is normally focal, diffuse infection causing renal failure can occur. Severe infection can cause papillary necrosis, particularly in patients with diabetes mellitus, who are also especially susceptible to emphysematous pyelonephritis if infection is with a gas-forming organism (often *E. coli*, a facultative anaerobe). This is a life-threatening infection that frequently necessitates nephrectomy. An abscess, either within the kidney or extending beyond the renal capsule (perinephric abscess) can form. This should be considered if the symptoms and signs of infection do not resolve with appropriate antibiotic treatment.

**Urethritis** – this presents with dysuria and urethral discharge. It is predominantly a sexually transmitted disease caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium* or *Trichomonas vaginalis*.

**Prostatitis** – this can be either acute or chronic depending on the duration of symptoms, and represents the most common recurrent UTI in men. It commonly presents with perineal or scrotal pain, frequency, urgency and dysuria.

### Symptomatic patients with a negative urine culture

It is not uncommon for patients to present with symptoms of UTI but a negative urine culture. Table 3 lists possible causes.

**Urethral syndrome** is an ill-defined syndrome, usually occurring in women who present with symptoms of UTI and fail to respond to antibiotics. It is important to exclude urethritis.

**Sterile pyuria** is the presence of white cells in the urine (with or without symptoms) in the absence of an identifiable uropathogen. Early morning urine samples should be sent to exclude mycobacterial infection. If pyuria persists, patients should be referred for urological assessment to exclude underlying causes such as urinary tract malignancy.

**Idiopathic interstitial cystitis** occurs in the absence of an identifiable cause. It presents with lower urinary tract symptoms that can be severe and debilitating.

### Diagnosis of UTI

A presumptive diagnosis of UTI can be made on the basis of the history and clinical examination, particularly when classical

### Causes of culture-negative urinary tract symptoms

- Antibiotics in urine
- Urinary tract malignancy
- Idiopathic interstitial cystitis
- Mycobacterial infection
- Schistosoma haematobium*
- Fungal infection
- Viral infection
- Fastidious organisms
  - *Chlamydia trachomatis*
  - *Mycoplasma hominis*
  - *Ureaplasma urealyticum*
  - *Gardnerella vaginalis*
- Inflammation
  - Cyclophosphamide
  - Post-irradiation
  - Bladder stone
  - NSAIDs

Table 3

features are present. However, only 68% of women presenting with a single symptom of cystitis (dysuria, cloudy urine, new nocturia) have a confirmed infection. Symptoms can be less specific in those aged >65 years; they include delirium but other causes of delirium should be sought if there are no other clinical features of UTI.

Urinary leucocyte esterase and nitrite (formed by conversion of nitrate to nitrite by most Gram-negative bacteria) and microscopic haematuria are found in 90%, 76% and 75% of patients with a culture-positive UTI, respectively. Urinalysis can therefore improve diagnostic precision when there is diagnostic uncertainty. It is not advisable to use urine dipsticks in the over-65s as the high false-positive rate makes them unreliable. Instead, Public Health England recommend sending urine for culture if the person is symptomatic and antibiotic treatment is planned.<sup>1</sup>

Microbiological analysis of the urine remains the gold standard for the diagnosis of UTI. The bacterial count (colony-forming units (cfu)), the type of bacterium isolated, its antibiotic sensitivities and the urinary white and red cell count per unit volume are reported. A bacterial count >10<sup>5</sup> cfu/ml is classically regarded as significant, but lower counts in patients with typical symptoms and in suprapubic aspirates are significant.

Treatment of uncomplicated cystitis with typical symptoms is usually started empirically, and urine culture and sensitivity testing are not required. However, urine culture should be sent before the first dose of antibiotics in all men with a suspected UTI. Urine culture is also important when infection is severe, complicated or recurrent and when the risk of treatment failure or resistance is higher. In the absence of clinical features, urine culture is indicated only in pregnant women and before urological intervention, when treatment may be indicated.

### Investigation

After the initial diagnosis, young women with symptoms that respond rapidly to treatment do not require investigation. Children, men (>1 infection), women with recurrent infection and patients

with severe pyelonephritis require further assessment. Ultrasonography, with estimation of post-micturition bladder residual urine, abdominal X-ray, urodynamics and cystoscopy, are used. Investigation of children is complex, depends on age at presentation, and includes micturating cystography and DMSA renography.

### Treatment

The natural history of cystitis is resolution of symptoms in 4–7 days. Antibiotic treatment is effective and reduces the duration of symptoms, whereas the benefit of non-antibiotic treatments, for example increased fluid intake, is unproven. Empirical treatment with 3 days of antibiotics achieves a cure in 85–90% of women with uncomplicated cystitis, which is equivalent to longer regimens and is more effective than a single dose. In the UK, trimethoprim or nitrofurantoin is recommended.<sup>1</sup> In non-pregnant women, delaying antibiotics for up to 48 hours to allow resolution of symptoms can reduce antibiotic use without significantly prolonging symptoms. Paracetamol can be used for symptom control, and patients should be advised to avoid dehydration by drinking enough fluid.<sup>1</sup>

For men, because of the increased likelihood of complicated infection and/or prostatitis, at least 7 days of treatment is recommended and antibiotics should be started immediately. Trimethoprim and nitrofurantoin are currently the first-line antibiotics. Quinolone antibiotics should be considered if prostatitis is suspected, but trimethoprim remains a suitable first-line agent.<sup>2,3</sup>

Milder forms of pyelonephritis can be treated with oral antibiotics, started empirically but reviewed in light of culture results. NHS Clinical Knowledge Summaries recommend 7 days of ciprofloxacin, co-amoxiclav or cephalexin or 14 days of trimethoprim for men and non-pregnant women, and 7–10 days of cefalexin for pregnant women. Treatment of more severe infections requires hospital admission for intravenous fluids and antibiotics, which can be given orally after clinical improvement and should be continued for up to 14 days.<sup>4,5</sup>

### Prevention of recurrent infection

Several interventions to reduce recurrent infections, such as increased fluid intake and complete bladder emptying, are used but unproven. The Cochrane review on the use of cranberries to prevent UTI concluded that cranberry preparations were not effective in reducing reinfection in young women. Trials of probiotic and oestrogen cream to re-establish normal vaginal/perineal flora have produced inconsistent results. Long-term, low-dose, nocturnal antibiotics and stand-by or post-coital antibiotics are effective for women with frequent infections.

### Antibiotic resistance

As with all bacterial infections, the rate of antibiotic resistance, including extended-spectrum  $\beta$ -lactamase production, among uropathogenic bacteria is increasing. The rates of antibiotic resistance of the common uropathogens in the UK are given in Table 4. *E. coli* is frequently resistant to oral penicillins and cephalosporins, but retains sensitivity to nitrofurantoin. Resistance to trimethoprim and quinolones has increased.

Patients with resistant isolates wait longer before symptom resolution, have higher re-consultation rates and have a greater need for multiple courses of antibiotics. It is important to consider previous sensitivities when prescribing in those with recurrent infections, and also to send urine for culture in those with risk factors for resistance such as care home residents, individuals with renal impairment or an abnormal urinary tract, those with recent travel to a country of increased resistance and patients who have been hospitalized for >7 days in the last 6 months.<sup>1</sup>

Resistance rates vary from region to region and depend on whether the infection develops in the community or in hospital. The National Institute for Health and Care Excellence (NICE) advises that each region should monitor resistance patterns on a regular basis.

### UTI in specific populations

**UTI in children** is common; 2% of children experience one UTI before the age of 10 years. Infection can prove difficult to diagnose, and urine collection for culture can be difficult. Prompt diagnosis, investigation and treatment of UTI are required to minimize the risk of renal scarring. Children with a combination of infection and reflux of urine from the bladder into the ureter and kidney are at particularly high risk of renal damage (reflux nephropathy). A group of diseases including reflux nephropathy (also called chronic pyelonephritis) and dysplastic kidneys accounts for 20% of renal failure in children, and contributes to hypertension and renal impairment in adults. The treatment and screening of children, especially young and male children, for reflux and other renal tract abnormalities depends on age and is detailed in NICE guidelines.

**UTI in pregnancy** can occur in up to 20% of pregnancies and is associated with an adverse outcome. Asymptomatic bacteriuria occurs during the first trimester in 2–9% of pregnant women, and symptomatic infection develops in 30% of these cases. Urine should be cultured at presentation, and bacteriuria (if confirmed in a second sample) treated with antibiotics.

**UTI in urology patients** is common. Bacteriuria develops in 5% of patients per day who have a urinary catheter and even short-term catheterization is associated with a 10% risk of UTI. Any structural abnormality predisposes to UTI, which can be recurrent and require long-term prophylactic antibiotics.

### Susceptibility to oral antibiotics among common uropathogenic bacteria

	Amoxicillin (% susceptible)	Cefradine (% susceptible)	Trimethoprim (% susceptible)	Nitrofurantoin (% susceptible)	Ciprofloxacin (% susceptible)
<i>Escherichia coli</i>	51	79	73	96	98
<i>Enterococcus faecalis</i>	100	—	—	100	—
<i>Klebsiella pneumoniae</i>	1	72	85	16	95
<i>Proteus mirabilis</i>	73	5	58	0	87

Table 4

**UTI in kidney transplant recipients** is the most common infection in the early post-transplant period; it is more likely to result from abnormal anatomy, catheterization and ureteric stenting than from immunosuppression. Acute pyelonephritis in a transplanted kidney should be treated promptly as it can lead to scarring in the transplant kidney. There is insufficient evidence to support giving antibiotics in cases of asymptomatic bacteriuria.

#### Rare infections of the urinary tract

**Mycobacterial infection** is rare in developed countries. It is difficult to diagnose and can cause progressive kidney damage without treatment.

**Fungal infections** are most commonly seen in association with diabetes mellitus, a structurally abnormal renal tract, or both. *Candida albicans* infection is the most common pathogen.

**BK virus infection** is caused by the small BK polyomavirus, which can affect the renal tract of severely immunocompromised patients, causing cystitis and nephropathy (particularly in the kidney transplant population).

**Schistosoma haematobium infection (bilharziasis)** is common in endemic areas. Early disease presents with symptoms of UTI and late-stage disease, typically with urinary tract obstruction caused by fibrotic strictures, and an increased risk of malignancy (squamous cell carcinoma). ◆

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## TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online [here](#).

### Question 1

A 60-year-old woman presented with a 24-hour history of dysuria and frequency. She had no urological past medical history and was usually fit and well.

On clinical examination, her temperature was 37.0°C. Suprapubic tenderness was noted.

#### What is the most appropriate next step in management?

- Do not offer antibiotics and do not perform urinalysis
- Perform urinalysis, and if positive, offer antibiotic treatment
- Offer antibiotics without performing urinalysis
- Offer antibiotic treatment after sending urine for culture but before waiting for the result
- Offer antibiotic treatment when the result of urine culture is available

### Question 2

A 31-year-old woman presented with a 2-day history of typical symptoms of cystitis. This was her third infection in the past 3 months, and both previous infections had been successfully treated with antibiotics.

#### What is the most appropriate next step in management?

- Advise regularly drinking cranberry juice to reduce risk of recurrent infection
- Advise topical oestrogen therapy to reduce risk of infection
- Do not offer antibiotic treatment, because of the risk of treatment failure
- Offer antibiotic treatment after sending urine for culture
- Offer antibiotic treatment without sending urine for culture

### Question 3

A 40-year-old man presented with dysuria and new nocturia. He had no scrotal pain or urethral discharge.

On clinical examination, his temperature was 37.0°C, and there was suprapubic tenderness. Urinalysis was positive for leucocytes and nitrites.

#### What is the most appropriate management?

- Send urine for culture and immediately start a 7-day course of trimethoprim
- Send urine for culture and immediately start a 3-day course of ciprofloxacin
- Test for gonorrhoea and chlamydia
- Give a 10-day course of ciprofloxacin and send for culture if treatment fails
- Send urine for culture and start a 7-day course of trimethoprim if the result is positive